

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF WISCONSIN

SAMUEL A. TEAGUE,

Plaintiff,

Case No. 18-cv-126-wmc

v.

DOCTOR HOFFMAN
AND NURSE STECKER,

Defendants.

JUDGMENT IN A CIVIL CASE

IT IS ORDERED AND ADJUDGED that judgment is entered in favor of defendants dismissing this case.

/s/

Peter Oppeneer, Clerk of Court

10/15/2020

Date



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Use of piperazine phenothiazine derivatives, or a pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament with neuroprotector and/or neurotrophic effects on CNS and/or PNS.

5

FIELD OF THE INVENTION.

This invention relates to a new use of piperazine phenothiazine derivatives and their pharmaceutically acceptable salts or esters in the manufacture of a medicament 10 with neuroprotector and/or neurotrophic effects on CNS and/or PNS.

BACKGROUND OF THE INVENTION

These compounds are known as major tranquilizers and 15 neuroleptic drugs for their effects as relieving schizophrenic agitation, and maniacal behaviour. More particularly the piperazine series which includes trifluoroperazine, prochlorperazine, flufenazine are the most potent phenothiazine antipsychotic compounds. Flufenazine is marketed 20 under the tradename Moditen® for its neuroleptic therapeutical effects. Fluphenazine and its hydrochloride salt or enanthate or decanoate ester form exerts activity at various levels of the CNS as well as on peripheral organ systems, which accounts 25 for its antipsychotic action and side effects. Indirect evidence indicates that the antipsychotic effects of phenothiazines are linked to their effect in blocking dopamine and other catecholamine receptor sites.

SUMMARY OF THE INVENTION

30 Surprisingly, the applicant has found that piperazine phenothiazine derivatives and more particularly flufenazine, are able to exert significant neuroprotective and neurotrophic effects. These new effects which could not be derived from

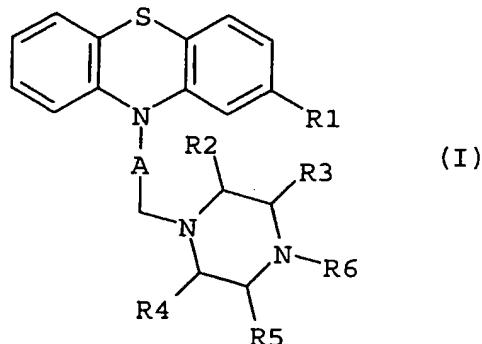
actual flufenazine antipsychotic action have been highlighted during specific in vitro and in vivo model studies of CNS and PNS neuronal degeneration.

5 The invention relates to

1. Use of piperazine phenothiazine derivatives, or a pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament with neuroprotector and/or neurotrophic effects on CNS and/or PNS.

10

2. Use according to item 1 wherein the piperazine phenothiazine derivatives are selected from compounds of formula I



15

wherein

A represents a straight or branched alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms ;

20 R1 represents hydrogen, halogen, lower alkyl, lower alkoxy, lower alkanoyl, lower alkyl-mercapto, trifluoromethylmercapto, lower alkyl-sulfonyl (preferably methylsulfonyl), perfluoro-alkyl of 1 to 3 carbon atoms;

R2, R3, R4 and R5 each represent methyl, ethyl or hydrogen,

25 R6 represents hydrogen, lower alkyl, hydroxy-lower-alkyl or aliphatic acyloxy-lower-alkyl having 1 to 4 carbon atoms in

the acyloxy portion and 1 to 6 carbon atoms in the alkyl portion, $\text{CH}_2\text{-CH}_2\text{-O-R7}$ where R7 represents hydrogen, COR8 where R8 is a branched or straight chain alkyl radical of from seven to fourteen carbon atoms;

5 in the manufacture of a medicament with neuroprotector and/or neurotrophic effects on CNS and/or PNS.

3. Use according to item 2 wherein

A represents ethylene, propylene or 2- methylpropylene;

10 R1 represents hydrogen, chloro, COCH_3 , $-\text{CF}_3$;

R2, R3, R4 and R5 each represent hydrogen;

R6 represents CH_3 , $\text{CH}_2\text{-CH}_2\text{-O-R7}$ where R7 represents hydrogen, COR8 where R8 is a straight chain alkyl radical of from seven to fourteen carbon atoms.

15

4. Use according to items 1 to 3, wherein the piperazine phenothiazine derivatives is flufenazine, or a pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament with neuroprotector and/or 20 neurotrophic effects on CNS and/or PNS.

5. Use according to items 1 to 4, in the manufacture of a medicament for the treatment of central and/or peripheral neurodegenerative diseases.

25

6. Use according to items 1 to 5, in the manufacture of a medicament for the treatment of Parkinson's disease.

7. Use according to items 1 to 5, in the manufacture of a 30 medicament for the treatment of Alzheimer's disease.

8. Use according to items 1 to 5, in the manufacture of a medicament for the treatment of peripheral neuropathy diseases.

5 9. Use according to item 8, in the manufacture of a medicament for the treatment of amyotrophic lateral sclerosis (ALS) diseases.

10. Use according to any one of items 1 to 9, wherein the medicament is for oral, rectal, subcutaneous, intramuscular or intravascular administration route.

15 11. Use according to any one of items 1 to 10, wherein the medicament comprises as active ingredient from 0,2mg to 500mg of the piperazine phenothiazine derivatives.

12. Use according to any one of items 1 to 11, wherein the medicament is administrated at doses comprised between 0.1mg/kg to 10mg/kg.

20

The invention provides also methods for the treatment of central and/or peripheral neurodegenerative diseases, of Parkinson's disease, of Alzheimer's disease, of peripheral neuropathy diseases or for the treatment of amyotrophic lateral sclerosis (ALS) diseases. The above methods comprise the administration to human or other animal subjects of an effective amount of piperazine phenothiazine derivatives compounds of formula I having neuroprotector and/or neurotrophic effects.

25

BRIEF DESCRIPTION OF THE FIGURES.

30 Fig 1: flufenazine effects on spinal cord neurons survival

Fig 2: protective effects on cortical neurons of flufenazine after glutamic acid intoxication and with maturation with BDNF.

Fig 3: protective effects of flufenazine on mesencephalic 5 neurons after MPP⁺ intoxication

Fig 4: neurotrophic effects of flufenazine on cortical neurons

Fig 5: neurotrophic effects of flufenazine on spinal cord neurons

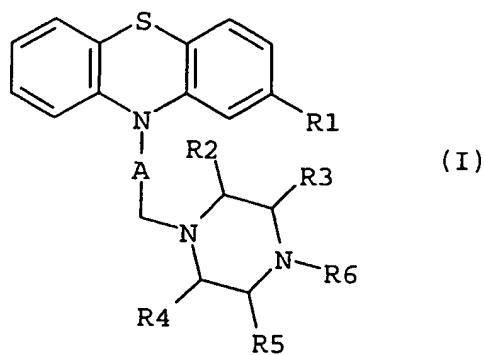
Fig 6: survival rate of SOD mice after oral administration of

10 flufenazine.

DETAILED DESCRIPTION

Thus, according to the present invention, there is provided the use of piperazine phenothiazine derivatives and a 15 pharmaceutically acceptable salt and /or ester thereof, in the manufacture of a medicament with neuroprotector and neurotrophic effects on CNS and PNS

Piperazine phenothiazine derivatives are defined as compounds 20 of the formula I



wherein

A represents a straight or branched alkylene chain of from 2 25 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms ;

R1 represents hydrogen, halogen (preferably chloro), lower alkyl, lower alkoxy, lower alkanoyl (preferably COCH_3), lower alkyl-mercaptop, trifluoromethylmercaptop, lower alkyl-sulfonyl (preferably methylsulfonyl), perfluoroalkyl of 1 to 3 carbon atoms, preferably CF_3 ;

R2, R3, R4 and R5 each represent methyl, ethyl or hydrogen;

R6 represents hydrogen, lower alkyl, hydroxy-lower-alkyl or aliphatic acyloxy-lower-alkyl having 1 to 4 carbon atoms in the acyloxy portion and 1 to 6 carbon atoms in the alkyl portion, $\text{CH}_2\text{-CH}_2\text{-O-R7}$ where R7 represents hydrogen, COR8 where R8 is a straight or branched chain alkyl radical of from seven to fourteen carbon atoms.

The terms "lower alkyl," "lower alkoxy", "lower alkanoyl" as employed herein include both straight and branched chain radicals of from 1 to 6 carbon atoms.

Preferably the piperazine phenothiazine derivatives used in the medicaments of the invention are selected from compounds of formula I wherein

A represents ethylene, propylene or 2-methylpropylene;

R1 represents hydrogen, chloro, COCH_3 , CF_3 ;

R2, R3, R4 and R5 each represent hydrogen;

R6 represent $\text{CH}_2\text{-CH}_2\text{-O-R7}$ where R7 represents hydrogen, COR8

where R8 is a straight chain alkyl radical of from seven to fourteen carbon atoms.

More preferably, the piperazine phenothiazine derivatives used in the medicaments of the invention is 4-[3-[2-(trifluoromethyl)-10H-phenothiazin-10-yl]propyl]-1-piperazine-ethanol (flufenazine) or salts and /or ester thereof.

These compounds and their chemical preparations under free bases form are disclosed in GB 829246, US 3.058.979.

This invention also includes salts of the above defined bases formed with non-toxic organic and inorganic acids.

Such salts are easily prepared by methods known in the art and are disclosed in GB 829246, US 3.058.979.

5 The invention also covers ester derivatives of the above compounds and their preparations are described in GB 833474 and US 3.194.733.

Thus, these documents, GB 829246, US 3.058.979, GB 833474 and
10 US 3.194.733 are hereby incorporated herein by references.

The medicaments of the invention are for treating central and peripheral neurodegenerative diseases as Parkinson's disease, Alzheimer's diseases or peripheral neuropathy diseases as
15 particularly amyotrophic lateral sclerosis (ALS) diseases.

The neuroprotective and neurotrophic effects of flufenazine were tested in vitro on primary neuronal cell cultures and in vivo, in animal model studies.

20 In vitro studies were first conducted on spinal cord motoneurons which are involved in peripheral neuropathy diseases as for example amyotrophic lateral sclerosis (ALS) according to protocols described by Martinou J.C., Martinou I., Kato A.C. in Cholinergic differentiation factor (CDF/LIF) 25 promotes survival of isolated rat embryonic motoneurons in vitro. Neuron 1992, 8(4) : 737-744) and by Ometani A, Nomoto H, Nitta A, Furukawa Y, Furukawa S. in 4-Methylcatechol stimulates phosphorylation of Trk family neurotrophin receptors and MAP kinases in cultured rat cortical neuron. J 30 Neurosci Res 2002 Nov 1;70(3):335-9.

Further studies were conducted on cortical neurons intoxicated with glutamic acid according to the protocol described by

Nilsen J. and Brinton RD in Impact of progestins on oestrogen-induced neuroprotection : synergy by progesterone and 19-norprogesterone and antagonism by medoxyprogesterone acetate. *Endocrinology* 143 : 205-212 2002.

5 Cortical neurons are involved in Alzheimer's disease and also in mesencephale neurons or dopaminergic neurons which are themselves involved in Parkinson's disease. (see also protocol described by Y. Mitsumotol, A. Watanabe, T. Miyauchi, F. Jimma, and T. Moriizumi in Stimulation of the regrowth of
10 MPP+/damaged dopaminergic fibers by the treatment of mesencephalic cultures with basigin ; *J Neural Transm* (2001) 108: 1127-1134).

In vivo studies were conducted on transgenic animals with ALS causing mutations, a model for neurodegenerative diseases
15 according to protocols described by Gurney Me, Pu H, Chiu Ay, Dal Canto Mc, Polchow Cy, Alexander Dd, Caliendo J, Hentati A, Kwon Yw, Deng Hx, et al. in Motor neuron degeneration in mice that express a human Cu ,Zn superoxide dismutase mutation. *Science* (1994) 264 : 1772-1775; and by Mohajeri Mh, Figlewicz
20 Da, Bohn Mc in Selective loss of alpha motoneurons innervating the medial gastrocnemius muscle in a model of amyotrophic lateral sclerosis. *Exp. Neurol.* (1998) 150 : 329-336.

All these tests demonstrate that neuronal survival increase in the presence of several concentrations of flufenazine compared
25 to the control without flufenazine and that flufenazine induces neuroprotective action after different intoxications.

The neurotrophic effect i.e. the neurite outgrowth with flufenazine was investigated on both cortical and spinal cord neuronal cultures according to the protocol described by
30 Lucius R, Sievers J. in Postnatal retinal ganglion cells in vitro: protection against reactive oxygen species (ROS)-induced axonal degeneration by cocultured astrocytes *Brain Res* 1996 Dec 16;743(1-2):56-62.

The results on neurite length as well as the percentage of cells with neurites quantified by careful microscopic inspection demonstrate the neurotrophic effect in the presence of several flufenazine concentrations compared to the control 5 without flufenazine.

The in vivo test results demonstrate the improved animals survival with the administration of several doses of flufenazine compared to the control without flufenazine.

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These medicaments can be administered by oral, rectal, subcutaneous, intramuscular or intravascular administration routes.

The medicaments according to the invention can be solids or 15 liquids and be presented in the pharmaceutical forms commonly used in human medicine, such as for example, plain or sugar-coated tablets, gelatin capsules, granules, suppositories, injectable preparations, ointments, creams, gels; they are prepared according to the usual methods. The active 20 ingredient(s) can be incorporated with the excipients usually used in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non aqueous vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various 25 wetting, dispersing or emulsifying agents, preservatives.

These compositions can in particular be presented in the form of a powder intended to be dissolved extemporaneously in an appropriate vehicle, for example apyrogenic sterile water.

The medicament can comprise as active ingredient from 0,2mg to 30 500mg of the piperazine phenothiazine derivatives.

The dose administered is variable according to the condition treated, the patient in question, the administration route and the product considered. It can be, for example, comprised

between 0,01mg and 50mg per day by oral route in adults with flufenazine or also comprised between 0.1 mg and 10mg per day by intramuscular or intravenous route.

5 Examples

In vitro studies:

Cell cultures conditions:

Two types of primary neuronal cell cultures i.e. cortical and spinal cord neurons are isolated from 15-17 days old foetuses 10 of female Wistar rats and cultured in neurobasal/B27 medium until cell differentiation.

Neuroprotection essays;

All tests are conducted with their appropriate control.

15

Example 1

Maintenance of neuronal survival and proliferation is a crucial process for the integrity of neurons. In the present study spinal cord motoneuron cell culture are used to assess 20 whether or not flufenazine promote neuronal survival and proliferation.

Neuronal survival and proliferation

Cells cultures are incubated with different Fluphenazine N-25 Mustard dihydrochloride concentrations: 50, 100, 250 nmol/l. Neuronal survival is then monitored at different time points; 2, 24, 48, 72, 96, 120 hours by counting the number of cells under microscope.

The results are depicted in Fig 1:

30 the percentage of neuronal survival obtained when cells cultures are incubated with flufenazine is compared to cell cultures incubated alone only with 50 microgram's of brain derived neurotrophic factor (BDNF). The whole percentages

increase regularly from 48h until 120h and the best survival results are obtained with flufenazine concentrations of 50 to 250 nmol/l.

5 Example 2

Glutamic acid intoxication assay:

The neuroprotective activity is assessed on glu-induced cortical neurons loss. The process of death is initiated by 10 min treatment of neuron cell cultures with neurotoxic 10 concentration of glutamic acid at 100 micromol/l.

The ability of flufenazine to reverse the death process is achieved by subsequent exposure of cells to flufenazine concentrations of 100 and 200nmol/l. The quantity of LDH released is used to estimate the degree of intoxication and 15 the decrease of quantity released is proportional at cellular resistance to Glu neurotoxicity.

The results are depicted in Fig 2 (right part):

the percentage of neuronal survival obtained when intoxicated 20 cells cultures are incubated with flufenazine is compared to cell cultures without flufenazine.

With 200nmol/l of flufenazine, a 10% increase is significantly observed.

In the left part of Fig 2, it can be observed that flufenazine has no or very slight effect, on cell survival in the absence 25 of neurotoxic compound.

Example 3

MPP+ intoxication essay:

The neuroprotective activity is assessed on MPP+ induced 30 mesencephalic neuron loss with flufenazine concentration of 250 nmol/l

The cells are intoxicated by 2 micromol of MPP⁺ as neurotoxic during 24h. The cell culture is then treated with 250nm/l of flufenazine. Reversed effects are observed after 48hours.

These neuroprotective effects are measured by the increased number of TH positive cells or dopaminergic neurons (i.e. mesencephale neurons which contains, tyrosine hydroxylase (TH), a dopamine synthesis enzyme.

The results are depicted in Fig 3 (right part):

The percentage of mesencephalic neuronal survival obtained when intoxicated cells cultures are incubated with flufenazine is compared to cell cultures without flufenazine.

With 250nmol/l of flufenazine, a 30% increase of TH positives cells is significantly observed.

These results show that flufenazine (250nmol/l) reverses MPP⁺ induced neuronal loss to the same extent as Riluzole (5 micromoles/l) a drug with established neuroprotective activity in this model (see reference Storch A, Burkhardt K, Ludolph AC, Schwarz J. Protective effects of riluzole on dopamine neurons: involvement of oxidative stress and cellular energy metabolism. J Neurochem 2000 Dec;75(6):2259-69).

In the left part of Fig 3, it can be confirmed that flufenazine according to its known extrapyramidal reactions has a negative effect (minus 50%) on the survival of this type of dopaminergic neurons.

In addition this assay also demonstrates longer neurite expansion than in control neurons at 250nmol/l).

30 Example 4

Neurotrophic assays:

The ability of flufenazine to induce neurite outgrowth is investigated both in cortical and spinal cord neuronal cultures after 24h exposure to flufenazine.

The neurite length as well as the percentage of cells with neurites are quantified by careful microscopic inspection.

On cortex neurons type, the results are depicted in Fig 4; the cortex neurotrophic effect of flufenazine (200nmol/l) is expressed as an increase of 30% on neurites length compared to the neurites length in the control cortex neurons

10 On spinal cord neurons, the results are depicted in Fig 5: The neurotrophic effect of flufenazine (50nmol/l, 100nmol/l) is expressed as an increase of 40 to 50% on neurites length compared to the neurites length in the control spinal cord neurons.

15

Example 5

In vivo assays.

Animals and flufenazine treatment.

Mice are used at 4 months of age i.e. about 2 weeks before the 20 appearance of the first symptoms.

They are genotyped for SOD1 gene using PCR method.

Animals are assigned into four groups to receive a daily oral administration of 1) saline as control, 2) 0,1mg/kg, 3) 1mg/kg, 25 4) 10mg/kg of flufenazine , until death by weakness and paralysis occurs.

Survival rate was recorded on a daily basis.

The results are depicted in Fig 6:

Doses of 0,1 and 1mg/kg flufenazine enhanced the survival of SOD mice as compared to that of the saline treated group. In 30 contrast, higher dose (10mg/kg) appeared to have an adverse effect and induced a leftward shift in the survival curve.

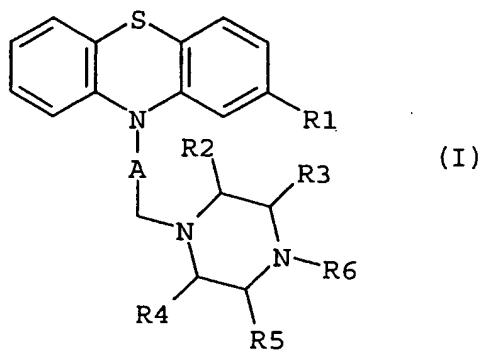
Claims.

1. Use of piperazine phenothiazine derivatives, or a pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament with neuroprotector and/or neurotrophic effects on CNS and/or PNS.

5

2. Use according to claim 1 wherein the piperazine phenothiazine derivatives are selected from compounds of

10 formula I



wherein

A represents a straight or branched alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms ;

15 R1 represents hydrogen, halogen, lower alkyl, lower alkoxy, lower alkanoyl, lower alkyl-mercaptop, trifluoromethylmercaptop, lower alkyl-sulfonyl (preferably methylsulfonyl), perfluoro-
20 alkyl of 1 to 3 carbon atoms;

R2, R3, R4 and R5 each represent methyl, ethyl or hydrogen,
R6 represents hydrogen, lower alkyl, hydroxy-lower-alkyl or aliphatic acyloxy-lower-alkyl having 1 to 4 carbon atoms in the acyloxy portion and 1 to 6 carbon atoms in the alkyl
25 portion, $\text{CH}_2\text{-CH}_2\text{-O-R7}$ where R7 represents hydrogen, COR8 where

R8 is a branched or straight chain alkyl radical of from seven to fourteen carbon atoms;

in the manufacture of a medicament with neuroprotector and/or neurotrophic effects on CNS and/or PNS.

5

3. Use according to claim 2 wherein

A represents ethylene, propylene or 2- methylpropylene;

R1 represents hydrogen, chloro, COCH_3 , $-\text{CF}_3$;

R2, R3, R4 and R5 each represent hydrogen;

10 R6 represents CH_3 , $\text{CH}_2\text{-CH}_2\text{-O-R7}$ where R7 represents hydrogen, COR8 where R8 is a straight chain alkyl radical of from seven to fourteen carbon atoms.

4. Use according to claims 1 to 3, wherein the piperazine

15 phenothiazine derivatives is flufenazine, or a pharmaceutically acceptable salt or ester thereof, in the manufacture of a medicament with neuroprotector and/or neurotrophic effects on CNS and/or PNS.

20 5. Use according to claims 1 to 4, in the manufacture of a medicament for the treatment of central and/or peripheral neurodegenerative diseases.

25 6. Use according to claims 1 to 5, in the manufacture of a medicament for the treatment of Parkinson's disease.

7. Use according to claims 1 to 5, in the manufacture of a medicament for the treatment of Alzheimer's disease.

30 8. Use according to claims 1 to 5, in the manufacture of a medicament for the treatment of peripheral neuropathy diseases.

9. Use according to claim 8, in the manufacture of a medicament for the treatment of amyotrophic lateral sclerosis (ALS) diseases.

5 10. Use according to any one of claims 1 to 9, wherein the medicament is for oral, rectal, subcutaneous, intramuscular or intravascular administration route.

11. Use according to any one of claims 1 to 10, wherein the
10 medicament comprises as active ingredient from 0,2mg to 500mg of the piperazine phenothiazine derivatives.

12. Use according to any one of claims 1 to 11, wherein the medicament is administrated at doses comprised between
15 0.1mg/kg to 10mg/kg.

Figure 1

Flufenazine effects on spinal cord neurons survival.

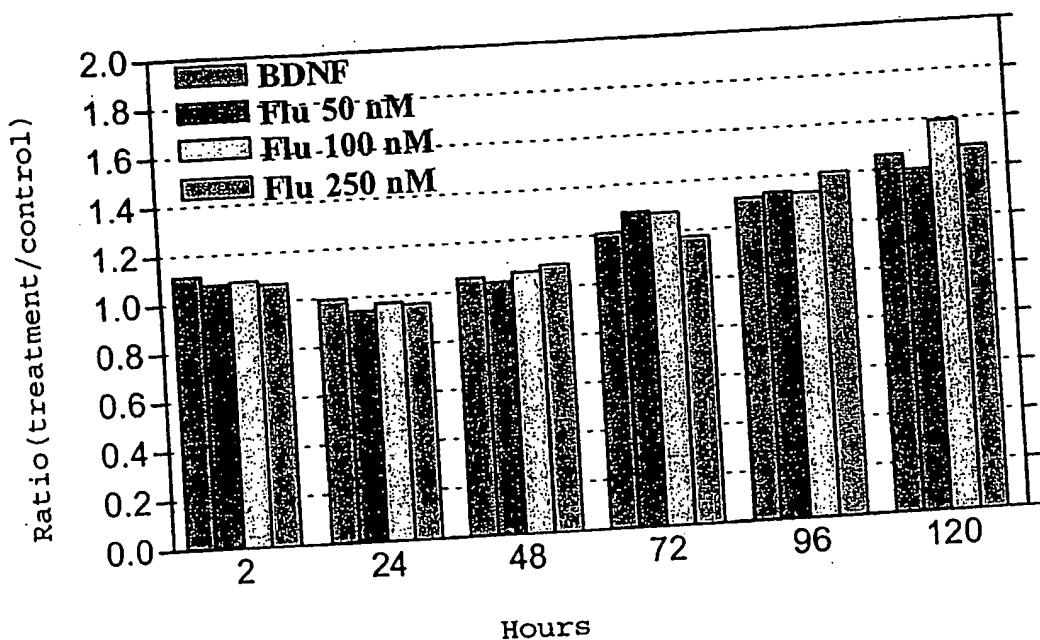


Figure 2

Protective effects on cortical neurons of flufenazine after glutamate intoxication and with maturation with BDNF.

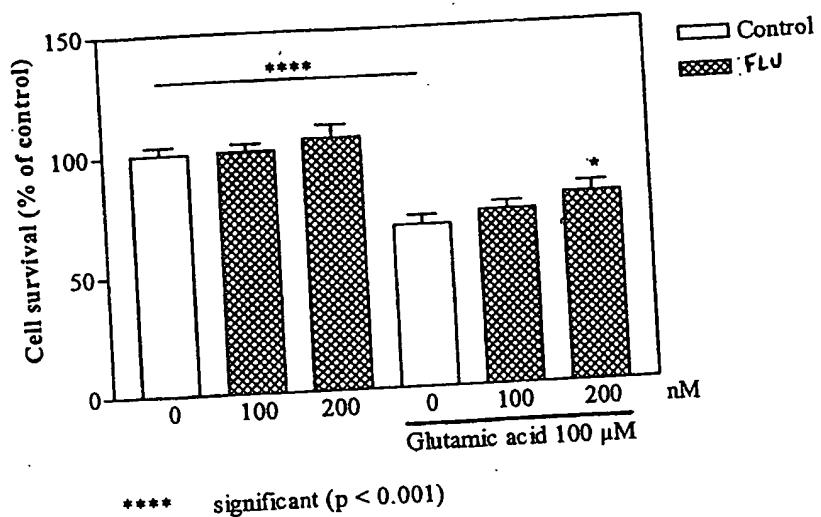
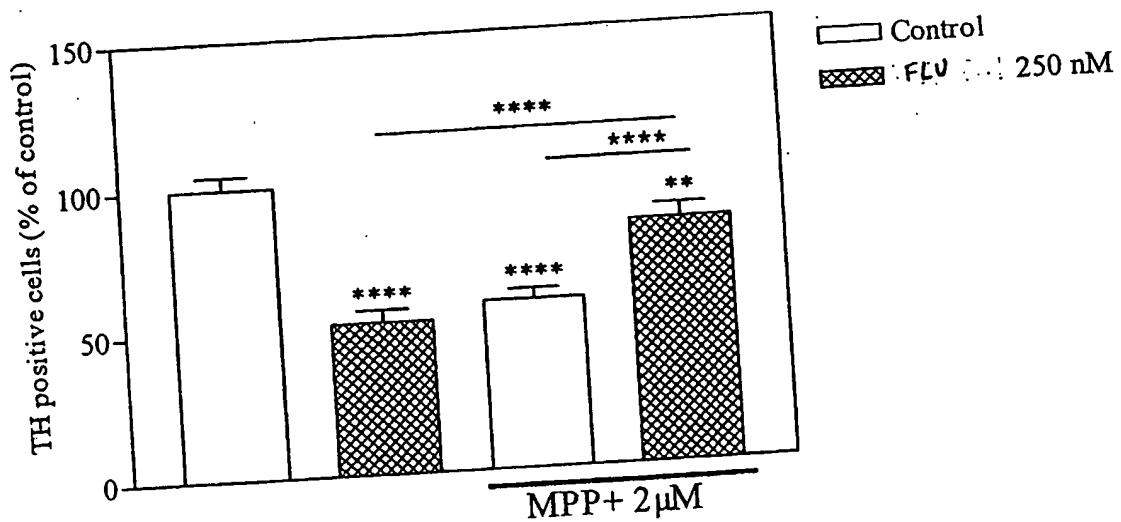


Figure 3

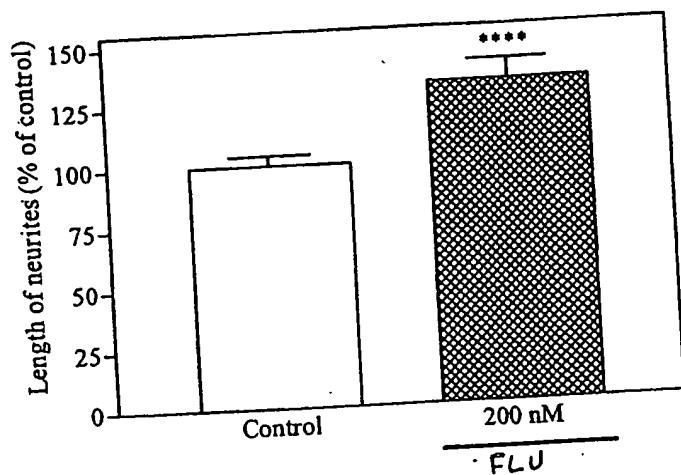
Protective effects of flufenazine on mesencephalic neurons
after MPP⁺ intoxication.



** significant from control ($p < 0.01$)
**** significant from control ($p < 0.001$)
_____ significant ($p < 0.001$)

Figure 4

Neurotrophic effects of flufenazine on cortical neurons.



**** significant from control ($p < 0.001$)

Figure 5

Neurotrophic effects of flufenazine on spinal cord neurons.

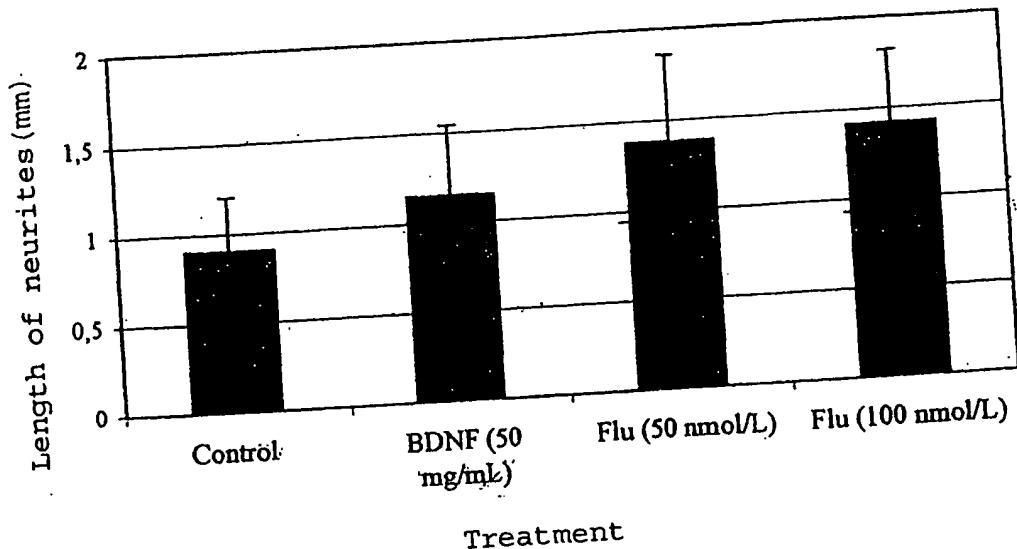
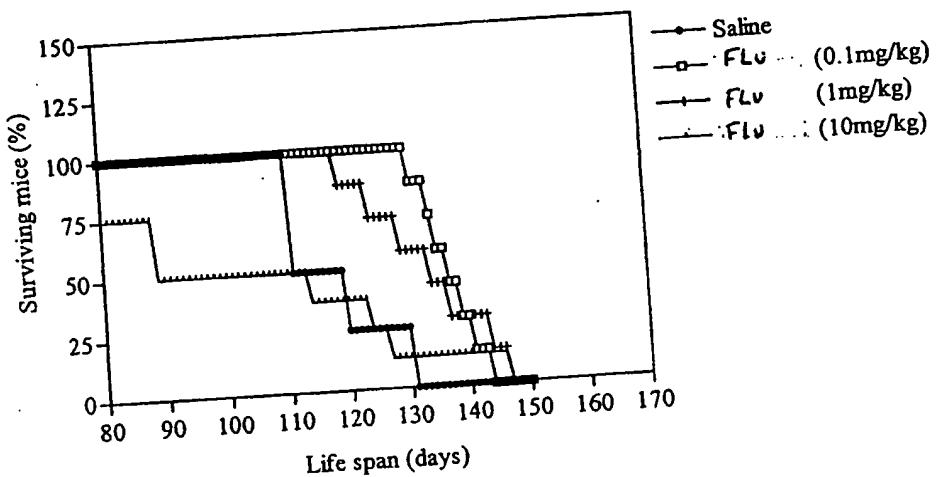


Figure 6

Survival rate of SOD mice after oral administration of flufenazine.



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/005183A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/5415 A61P25/28 A61P25/16 A61P25/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HALE M S ET AL: "LOW DOSE PERPHENAZINE AND L DOPA CARBIDOPA THERAPY IN A PATIENT WITH PARKINSONISM AND A PSYCHOTIC ILLNESS", JOURNAL OF NERVOUS AND MENTAL DISEASE, vol. 168, no. 5, 1980, pages 312-314; XP008020514 ISSN: 0022-3018 the whole document	1-3, 5, 6, 10-12
X	PERINI M ET AL: "BENEFIT OF FLUOPERAZINE IN DRUG-INDUCED HALLUCINATIONS DURING PARKINSON'S DISEASE MANAGEMENT", GAZZETTA MEDICA ITALIANA ARCHIVIO PER LE SCIENZE MEDICHE, vol. 148, no. 3, 1989, pages 101-104, XP008020513 ISSN: 0393-3660 abstract	1-3, 5, 6, 10-12

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

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T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the International search

29 November 2004

Date of mailing of the International search report

22.12.2004

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/005183

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 320 245 A (MILTON WOLF ET AL) 16 May 1967 (1967-05-16) column 1, line 15 - line 22; claims; examples -----	1,5,6, 10-12
X	US 3 320 249 A (JACK BERNSTEIN) 16 May 1967 (1967-05-16) column 2, line 60 - line 64; claims; example 11 -----	1,5,6, 10-12
X	US 6 482 822 B1 (AUVIN SERGE ET AL) 19 November 2002 (2002-11-19) column 1, line 40 - line 46; example 22 -----	1,5-12
X	WO 99/07356 A (SANBERG PAUL RONALD ;SHYTLE ROLAND DOUGLAS (US); SILVER ARCHIE AAR) 18 February 1999 (1999-02-18) abstract; claims 1,5,6,8 -----	1-6, 10-12
X	EP 0 615 749 A (UNIV VIRGINIA COMMONWEALTH) 21 September 1994 (1994-09-21) abstract column 5, line 51 - column 6, line 3 -----	1-5,8, 10-12
Y	VERMA ANITA ET AL: "N-Methyl-D-aspartate receptor participation in Parkinson's disease, a neurodegenerative disorder." ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, vol. 765, 1995, page 327, XP008020512 Second International Conference;Lake George, New York, USA; July 31-August 3, 1994, Clinical and experimental aspects. 1995 New York Academy of Sciences 2 East 63rd Street, New York, New York 10021, USA ISBN: 0-89766-946-0 the whole document -----	1-6, 10-12
Y	US 6 057 373 A (FOGEL BARRY S) 2 May 2000 (2000-05-02) abstract column 3, line 45 - line 56 column 10, line 42 - line 46; claims -----	1-6, 10-12
A	"THE MERCK INDEX" 2001, MERCK & CO., INC. , XP002254640 page 3780 No. 3783: Ethopropazine -----	1-6, 10-12
X	WO 01/78709 A (MINERVA BIOTECHNOLOGIES CORP) 25 October 2001 (2001-10-25) page 5, line 9 - page 6, line 22 * page 25, compoung G *claims 1-7,35,36,41,53,55,56; figure 3 -----	1-8, 10-12
		-/-

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP2004/005183

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96/04915 A (EINSTEIN COLL MED ;DAVIES PETER (US); VINCENT INEZ J (US)) 22 February 1996 (1996-02-22) abstract; claims -----	1-5,7, 10-12
X	GOTTLIEB G L ET AL: "Depot neuroleptics in the treatment of behavioral disorders in patients with Alzheimer's disease." JOURNAL OF THE AMERICAN GERIATRICS SOCIETY. UNITED STATES JUL 1988, vol. 36, no. 7, July 1988 (1988-07), pages 619-621, XP008026221 ISSN: 0002-8614 the whole document -----	1-5,7, 10-12
X	WO 00/24390 A (LAM FRED CHIU LAI ;UNIV BRITISH COLUMBIA (CA); REINER PETER B (CA)) 4 May 2000 (2000-05-04) abstract; claims 1,11,12,15,16,20,21,24,29,30 -----	1-3,5,7, 8,10-12
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X	WO 00/32175 A (PFIZER PROD INC) 8 June 2000 (2000-06-08) page 23 page 31, line 25 - line 31; table 1 claims -----	1,5,7, 9-12
X	WO 01/92240 A (MCDONALD ROBERT S ;MARTIN EARL V (CA); DARVESH SULTAN (CA); MAGEE) 6 December 2001 (2001-12-06) page 6, line 15 - line 19 page 20; table 1 claims 26-31; example 18 -----	1,5,7, 10-12
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Intern	al Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 03/062232 A (SCRAS ;DOLO CHRISTINE (FR); CHABRIER DE LASSAUNIERE PIERRE (FR); H) 31 July 2003 (2003-07-31) page 17, line 10 – line 15; claims 1,7,11-13; example 14 page 5, line 7 – line 25 -----	1,5-12
P, X	WO 03/062388 A (UNIV CALIFORNIA) 31 July 2003 (2003-07-31) paragraph '0041! page 29; claims 1-5; figure 3 -----	1-3,5-7, 10-12

INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5 (partly), 6, 10-12 (partly)

Use of piperazine phenothiazine derivatives in the manufacture of a medicament for treating Parkinson's disease

2. claims: 1-5 (partly), 7, 10-12 (partly)

Use of piperazine phenothiazine derivatives in the manufacture of a medicament for treating Alzheimer's disease

3. claims: 1-5 (partly), 8, 10-12 (partly)

Use of piperazine phenothiazine derivatives in the manufacture of a medicament for treating peripheral neuropathy diseases

4. claims: 1-5 (partly), 9, 10-12 (partly)

Use of piperazine phenothiazine derivatives in the manufacture of a medicament for treating amyotrophic lateral sclerosis diseases

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